HAE in Special Populations
A Focus on Women

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Disclosure

- Stocks: Merck
- Consultant/Advisory Board: Merck, AstraZeneca, Alcon, GlaxoSmithKline, Genentech, ISTA, Sanofi US, Novartis, CSL Behring, ViroPharma
- Speaker: Merck, AstraZeneca, Alcon, GlaxoSmithKline, Genentech, ISTA, Sanofi US, Novartis, Teva, CSL Behring, ViroPharma, Shire
- Honorarium: Merck, AstraZeneca, Alcon, GlaxoSmithKline, Genentech, ISTA, Sanofi US, Novartis, Teva, CSL Behring, ViroPharma
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Learning Objectives

Upon completion of this session, participants should be able to:

- Identify special needs of children and women with hereditary angioedema (HAE)
- Discuss unique management requirements in special populations of HAE

Special Populations in HAE

- Overview
- Site of care
- Children / Teenagers
- Women
  - Androgen treatment in women
  - Pregnancy
  - Breastfeeding
  - Menopause

Overview of HAE

Parameter	HAE Type		
	I	II	III
Percent of all HAE	85	15	Rare
C1-INH Antigenic Level	Low	Normal	Normal
C1-INH Functional Level	Low	Low	Normal
C4	Low	Low	Normal

Type III

- Clinical diagnosis
- Mostly women
- Association with Factor XII
- Genetic polymorphisms
- Diversity of clinical phenotypes

Individualization of HAE Therapy

Patient factors

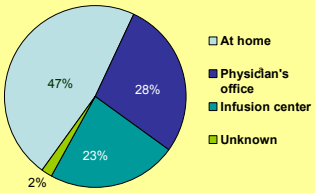
- Type / pattern of attacks
- Patient preference
- Quality of life
- Age
- Sex
- Access to medical care
- Other Medical Problems

Medication factors

- Efficacy and safety
- Route of administration
- Treatment complications
- Availability
- Contraception / HRT
- ACE inhibitors
- Cost
- Site of care

Site of Care in HAE Patients Using C1-INH-nf

- 516 patients in USA
- 47% of patients received therapy at home
- 20% of patients self-administered



Home includes: self-administration, administration by home health agencies and administration by family

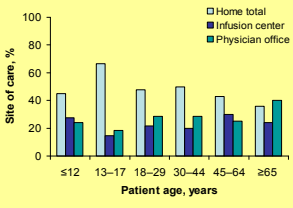
C1-INH-nf, nanofiltered C1 inhibitor
Landmesser L, *et al.* ACAAI 2010: Poster presentation.

Gender Affects Site of Care for C1-INH-nf

- Males and females reported similar results for site of care
- Females less likely to receive help from family member (6.3% vs. 12.1% for males)

Landmesser L, *et al.* ACAAI 2010: Poster presentation.

Site of Care Differs Among Age Groups



- Majority of adolescents reported home administration
- Patients 30–44 most likely to self-administer
- Patients ≥65 more likely to receive therapy at physician offices or home health agencies
- No patients ≤12 or ≥65 reported self-administration

Home total includes: self-administration, administration by home health agencies and administration by family

Landmesser L, *et al.* ACAAI 2010: Poster presentation.

Home Administration of C1-INH-nf

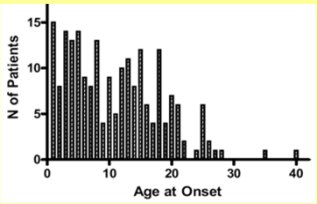
- Demonstrated ability to self / partner infuse allows:
  - Increased QoL
  - Increased flexibility & convenience
  - Decreased time to treatment
  - Decreased severity / duration of attacks
  - Decreased costs
- 2 studies document patient benefits:
  - Increased QoL (Bygum et al, Europe Jnl Derm, 2009)
  - Feasible and safe (Levi et al, JACI, 2006)
- Correct patient selection and training required to achieve reasonable and effective results

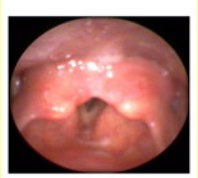
Dagen and Craig; AACI; 2010, 6:11

HAE in Children / Teenagers

PEDIATRIC CARE OF HAE

- Onset of symptoms occurs during childhood in majority of cases
- Anatomical characteristics require special considerations when establishing diagnosis and management
- 1 mm edema reduces airway diameter
  - 27% in adults, 44% in children, 75% in neonates





Bork K, et al. *Am J Med*. 2006;119:267-274; with permission.

Farkas H. *Allergy Asthma Clin Immunol* (AACI 2010). 2010;6(1):19.

PEDIATRIC CARE OF HAE
Clinical Manifestations

Onset of Symptoms
- 5 - 11 yo
- early onset of symptoms may mean more severe course of HAE
- symptoms may increase during adolescence

Gastrointestinal edema
- may mimic acute abdomen
- celiac disease more common in HAE
- estimating prevalence of GI edema difficult ('belly ache')

Upper airway edema
- occurs between ages 11 - 45 years
- asphyxia may ensue more rapidly in children because of smaller airway diameter

Bygum A. Br J Dermatol 2009; 161(5):1153-8.

PEDIATRIC CARE OF HAE
Diagnosis

COMPLEMENT TESTING
- C' levels influenced by age, birth weight, and gestational age
- Antigenic and functional C1-INH levels correspond to 70% and 61.8% of adult values initially and increase to normal level by age 6-12 mo
- Initial screening 6-12 mo

GENETIC TESTING
- Not routinely used in clinical practice, is expensive and available in few health care centers
- No mutation of the C1-INH gene detected in 8-10 % of cases

Pappalardo E, Caccia S, Suffritti C, Tordai A, Zingale LC, Cicardi M. Mol Immunol 2008; 45(13):3536-44.

PEDIATRIC CARE OF HAE
Management

- Teachers and health care personnel should be informed in writing
- Attacks can be decreased with appropriate counseling and lifestyle modifications reducing trigger factors
  - Stigmatization by peers more frequent in children than in adults
- Trigger Factors
  - Differ slightly in pediatric patients
    - ✓Infection and trauma more common
  - Menarche onset earlier
  - Medications
    - ✓Early use of contraception more common
    - ✓Treatment with ACE- I less common
  - Vaccinations for children safe
    - ✓Prevention of infections may reduce frequency of attacks
- Medication should be available at all times

Farkas H, Varga L, Szeplaki G, Visy B, Harmat G, Bowen T. Pediatrics 2007; 120(3):e713-22.
Farkas H. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1)

PEDIATRIC CARE OF HAE
Acute Attacks

- C1-INH-pd concentrate effective and safe
- Minimal experience available with these drugs:
  - Bradykinin receptor B2 antagonist (<12 years)
  - Kallikrein inhibitor (<16 years)
  - Recombinant C1-INH concentrate
- Extremity and mild abdominal attacks may be controlled with increased doses of AF or AA

AF- antifibrinolytics AA –attenuated androgens

Farkas H. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1)

PEDIATRIC CARE OF HAE
Short Term Prophylaxis

Drugs and indications same as adults

SHORT-TERM PROPHYLAXIS
- Short term prophylaxis required less; surgical interventions less frequent and shorter duration
- Alternating short term prophylaxis with double doses of TXA or AA may be warranted in presence of symptoms

INTERMITTENT PROPHYLAXIS
- AF, AA, and C1-INH-pd may be administered over a few months when starting school, during exam periods, flu season, family crises, and puberty

TXA - tranexamic acid

Farkas H, Jakab L, Temesszentandrasi G et al. J Allergy Clin Immunol 2007; 120(4):941-7.
Farkas H. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1)

PEDIATRIC CARE OF HAE
Long Term Prophylaxis

Drugs and indications same as adults

- Most children do not require long-term prophylaxis
- AF preferred to AA because of safety profile
- TXA better tolerated than EACA
- AA may be used, however
  - AA may cause liver damage and atherogenesis
  - masculinization and hypogonadism may occur in boys and menstrual irregularities in girls
  - behavior effects common
  - reduction in final height may occur from premature closure of epiphyseal plates
  - undesirable effects can be avoided via monitoring and reviewing ongoing therapy and using lowest effective dose

EACA - epsilon aminocaproic acid

Craig TJ. Allergy Asthma Proc 2008; 29(3):225-31.
Farkas H, Harmat G, Fust G, Varga L, Visy B. Pediatr Allergy Immunol 2002; 13(3):153-61.
Church JA. Ann Allergy Asthma Immunol 2004; 92(3):377-8.

PEDIATRIC CARE OF HAE
Home Treatment

- Allows timely intervention
- Eliminates delays in intervention
- Medication is best administered by health care professionals
- Consultation with physician important - diagnosis is challenging

Bygum A, Andersen KE, Mikkelsen CS. Eur J Dermatol 2009; 19(2):147-51.
Martinez-Saguer I, Rusicke E, Aygören-Pürsün E. Presentation ACAAI 2009. Miami, Florida, USA, 2009.
Aygören-Pürsün E, Martinez-Saguer I, Rusicke E, Klingebiel T, Kreuz W. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1):21

PEDIATRIC CARE OF HAE
Monitoring

- Follow up visit recommended at least once a year
- Newly diagnosed patients and those on long term prophylaxis should be seen at 3-month intervals initially and then twice a year for next 2 years
- Follow up visits should include:
  - recording of symptoms, acute treatments used, and side effects of therapies
  - laboratory testing as appropriate
  - clinical assessments; abdominal US if patient treated with androgens

Church JA. Ann Allergy Asthma Immunol 2004; 92(3):377-8.
Farkas H, Harmat G, Fust G, Varga L, Visy B. Pediatr Allergy Immunol 2002; 13(3):153-61.

HAE Care in Women

LKW 2011 with permission

HAE Case Presentation (AB)

- 27 yo African American female diagnosed age 10 after menarche with sx's of abdominal pain and swelling
- Abdominal attacks 3-4 times a month and monthly extremity swelling; two upper airway episodes
- PMH: food allergies
- FMH: 5 family members have HAE
- Social: missed work due to attack frequency and severity
- Labs:
  - C4 – 8 (norm: 10-40 mg/dL)
  - C1-INH func – 18 (norm >67%_
  - C1-INH quant – 6 (norm 19-37 mg/dL)
- Rx: on demand C1-INH-pd at age 24; C1-INH-nf at age 25
- Current Meds:
  - C1-INH-nf 1000 units 2x week and is improved
  - C1-INH-pd 1000 units infrequently

Question 1

Which of the following treatments are FDA approved for children <11 yo with HAE?

A) Attenuated androgens
B) Antifibrinolytics
C) C1-INH
D) None of the above

Question 2

What treatment is FDA approved for acute HAE attacks in 14 yo females?

A) C1-INH plasma derived
B) Ecallantide
C) Icatibant
D) C1-INH recombinant

Question 3

AB becomes pregnant and has increased HAE attacks. What is the safest treatment available for her?

A) Ecallantide
B) Anti-fibrinolytics
C) C1-INH
D) Attenuated androgens

HAE Care In Women

General

- Anatomical / physiological / hormonal changes may
  - influence the manifestations of HAE
    - ✓ menarche, estrogen contraception, pregnancy, menopause
  - interfere with the diagnosis of HAE
- Special diagnostic procedures may be required
- Range of products available for safe therapy is limited due to adverse effects

Agostoni A, Medicine (Baltimore).1992 Jul;71(4):206-15.,
Farkas H, Eur J Clin Pharmacol. 2010 Apr;66(4):419-26.
Bork K, Ann Allergy Asthma Immunol. 2008 Feb;100(2):153-61. 1:
Bouillet L. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1):17.

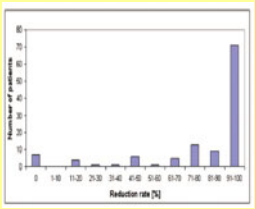
HAE CARE IN WOMEN

Family Planning

- Contraception
  - Estrogens should be avoided – can worsen the natural course of HAE. Barrier methods, progesterone, and IUD preferred
- Prophylaxis with AF should be discontinued days before attempting to conceive
- Prophylaxis and acute treatment with C1-INH-pd may be continued
- Prophylaxis with AA
  - Should be stopped 2 months before attempted conception due to risk of abnormalities in fetus
  - If patient becomes pregnant, AA should be discontinued and family informed about risk of fetal abnormalities

Bouillet L Am J Obstet Gynecol. 2008
Pilbrant A, Schannong M, Vessman J. Eur J Clin Pharmacol 1981;20:65-72

Efficacy of Androgens for Long-Term Prophylaxis in HAE



58 of 118 subjects discontinued androgen therapy: 41 due to adverse effects, 7 due to inefficacy

Bork K, et al. *Ann Allergy Asthma Immunol*. 2008;100:153-161, with permission.

Contraindications of Androgens

- Pregnancy
- Lactating women
- Hepatic disease (HCV hepatitis, etc)
- Children (before Tanner stage V)
- CA (prostate / breast)
- Nephrotic syndrome

HAE Care in Pregnancy

Diagnosis

Manifestations of HAE may first occur during pregnancy

- Complement testing
  - Plasma C1-INH level decreases during pregnancy as a consequence of increased plasma volume
  - Patients with eclampsia / pre-eclampsia have lower levels of C1-INH during third trimester
  - Low C1-INH levels return to normal after delivery → repeat C1-INH testing is necessary after delivery to confirm diagnosis of HAE
- Genetic testing rarely recommended

Hsieh FH, Allergy Asthma Proc. 2002 Mar-Apr;23(2):157-61.
Cunningham DS, J Reprod Med. 1991 Apr;36(4):312-3;
Obtulowicz K, The 6th C1-INH Deficiency Workshop, May 2009, Budapest

HAE Care in Pregnancy

Prenatal Diagnosis of Infant

Routine use of prenatal diagnostics not necessary

- No mutation of the C1-INH gene can be detected in 8 -10% cases
- Mutation is not a valid indication for terminating pregnancy because:
  - – HAE is a manageable disease
  - – Severity cannot be predicted in advance
- A prenatal diagnostics team consisting of ultrasound imaging specialists, perinatologists, gynecologists, geneticists, and HAE specialists should be established
- If fetus has C1-INH deficiency the number of maternal attacks may / may not increase during last trimester, but C1-INH activity level is lower in the plasma of mothers pregnant with a fetus affected by HAE

Kalmar L, Hum Mutat 2003; 22:498, Pappalardo E, Mol Immunol. 2008 Aug;45(13):3536-44.
Martinez Am J Obstet Gynecol 2010 Czaller Eu J Obstet Gynecol Reprod Biol 2010,

HAE Care in Pregnancy
Symptoms

PREGNANCY

- Variable impact
- Attacks most severe during 1st trimester and occur with highest frequency in 3rd trimester
- Attack frequency observed during previous pregnancies does not predict events during any subsequent pregnancy
- Early onset of initial symptoms associated with increased frequency and severity of attacks
- Abdominal attacks occur more frequently

Bouillet. Allergy, Asthma & Clinical Immunology. 2010,6:17
Obtulowicz K, Porebski G, Bilo B,The 6th C1-INH Deficiency Workshop May 2009, Budapest

HAE Care in Pregnancy
Symptoms

Spontaneous abortion and premature labor:

- No increase in incidence; however, a study reported more frequent occurrence

Labor and delivery:

- Rarely induce attacks which may occur either during labor or within 48 hours of delivery
- After childbirth, incidence of local vulvar swelling exceeds that of genital edema experienced before pregnancy
- The proportion of Caesarean sections is not higher than in the general population

Bork K, Am J Med. 2006 Mar;119(3):267-74;
Bouillet L Am J Obstet Gynecol. 2008 Nov;199(5):484.e1-4

HAE Care in Pregnancy
Treatment of Attacks

- C1-INH-pd recommended as first line therapy for HAE in pregnancy
  - Safe and effective during both pregnancy and lactation
  - Dose adjustment not necessary
- No experience available with newer drugs (bradykinin receptor B2 antagonist, kallikrein inhibitor, recombinant C1-INH)
- FFP – risks and precautions similar to non-pregnancy
- AF may be administered for mild acute attacks during pregnancy

FFP – fresh frozen plasma
Farkas H, J Allergy Clin Immunol. 2007 Oct;120(4):941-
Gooi JHC, Shillito J.The 6th C1-INH Deficiency Workshop, May 2009, Budapest

HAE Care in Pregnancy

Short Term Prophylaxis

C1-INH –pd drug of choice. If not available, FFP or AA may be administered

- Amniocentesis / chorionic villous sampling
- Surgical abortion
- Dilatation and curettage
- Hospital delivery recommended
- Routine administration before uncomplicated natural delivery is not recommended, but C1-INH-pd should be immediately available. C1-INH concentrate is recommended before labor and delivery when HAE is severe
  - Administration of C1-INH-pd recommended if forceps or vacuum delivery
  - After vaginal delivery patients should be monitored carefully for 48 hours postpartum
- Cesarean section- epidural anesthesia and prophylaxis with C1-INH-pd recommended
- Close follow up recommended for at least 72 hours postpartum after routine vaginal delivery and for one week after Caesarean section

Czaller Eu J Obstet Gynecol Reprod Biol 2010, Martinez Am J Obstet Gynecol 2010

HAE Care in Pregnancy

Long Term Prophylaxis

DRUG PROPHYLAXIS

- C1-INH-pd concentrate safe and effective during pregnancy and lactation
- Anti-fibrinolytics to be used when pd C1-INH is unavailable. AF's cross the placenta. They are not teratogenic in animals, but are excreted into breast milk. These drugs are not recommended during breastfeeding.
- AA not recommended since they cross placenta causing masculinization of the female fetus, placental insufficiency, and fetal growth retardation. Excretion into breast milk is unknown. Discontinuation of breastfeeding before the introduction of AA is recommended – terminating lactation itself may reduce attack frequency.

Czaller Eu J Obstet Gynecol Reprod Biol 2010
Martinez Am J Obstet Gynecol 2010
Galan HL, J Reprod Med. 1996 Jul;41(7):541-4.
Prematta M, Ann Allergy Asthma Immunol. 2007 Apr;98(4):383-8

HAE in Women

Breastfeeding and Menopause

Breastfeeding

- May be associated with increased attacks
  - Mainly abdominal symptoms & facial edema
- TXA, danazol and icatabant secreted in breast milk

Menopause

- ~55% have no change in symptoms
- 33% worsen
- 13% improve

Bouillet. Allergy, Asthma & Clinical Immunology. 2010, 6:17

Conclusions

- Therapeutic goal is to minimize disruption, disability, and death
- An individualized approach to HAE therapy in special populations is necessary
  - No treatment
  - Episodic care indicated when appropriate
  - Prophylaxis should be considered for patients meeting selected criteria
- Treatment guidelines are evolving